(c)   assaying for the presence of circulating IgG anti-HLA Class II antibodies

in the serum of the recipient;

wherein the presence of activated T-lymphocytes in the recipient and the presence of circulating

IgG anti-HLA Class II antibodies in a DR mismatched recipient indicates a high risk of

transplantation rejection.

Please amend claim 19 as follows:

19.   (amended) A method for predicting whether or not a transplant recipient is likely

to reject a tissue allograft comprising detection of IgG anti-HLA DR antibodies in

the serum of the recipient against a panel of control B lymphocytes wherein

detection of such antibodies indicates that the recipient is likely to reject a tissue

allograft.

REMARKS

Claims 1-7 and 19 are currently pending. Claims 1-7 and 19 are rejected under 35

U.S.C. §112, second paragraph, as being indefinite. Claim 19 is rejected under 35 U.S.C.

§102(a) and (b) and §103(a). Applicant has amended the claims to more particularly claim the

subject matter of the invention.

For reasons detailed below, the rejection should be withdrawn and the claims

allowed to issue. Entry of the foregoing amendments is respectfully requested.

1. The Claims are Definite as Required by 35 U.S.C. 112, Second Paragraph

Claims 1-7 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention.

The Examiner alleges that in claim 1, part (a) "the donor" lacks antecedent basis. Applicant has amended claim 1 to correct the antecedent basis of "the donor" in step (a). Specifically, step (a) has been amended to read as follows: "(a) determining the HLA-DR of the recipient and the HLA-DR of a donor and determining if the recipient and donor are DR mismatched;"

The Examiner alleges that in claim 19, line 4 "a recipient" is unclear. Applicant has amended claim 19 to correct the antecedent basis of "a recipient."

In view of these amendments and remarks, the rejections under 35 U.S.C. §112, first paragraph, should be removed.

2.   Claim 19 is Not Anticipated

Claim 19 is rejected under 35 U.S.C. 102(a) as being entirely anticipated by Itescu et al. (Circulation, 98 (8), 786, 1998;"Itescu"). The Examiner maintains that Itescu provides a verbatim disclosure of Example 7 of the specification, which teaches the method of claim 19.

Applicant maintains that contrary to the Examiner's assertion, provisional application no. 60/090153 ("the '153 application"), filed on June 22, 1998 fully supports the subject matter of claim 19, i.e., a method for predicting whether or not a transplant recipient is likely to reject a tissue allograft based on detection of IgG anti-HLA DR antibodies. Specifically, page 12, lines 7-22 of the '153 application discloses that IgG anti-MHC class II antibodies are associated with progression to high grade cellular rejection (see also Table 3). Since the Itescu was published after the June 22, 1998 filing date of the '153 patent application, Itescu cannot be prior art under 35 U.S.C.§102(a).

Anticipation "requires that all the elements and limitations of the claim be found within a single prior art reference...there must be no difference between the claimed invention

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and the reference disclosed, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.* 927 F2d 1565, 18 U.S.P.Q. 2d 1001, 18 U.S.P.Q. 2d 1896 (1991).

Claim 19 is also rejected under 35 U.S.C.§102(b) as being anticipated by Ten Hoor et al. (Transplantation, 56,298, 1993: "Ten Hoor"). According to the Examiner, Ten Hoor shows that the presence of IgG anti HLA-DR specific antibodies in serum of a prospective transplant recipient indicates that the recipient is likely to reject an allograft within one year.

Applicant has amended claim 19 to indicate that the claimed method is directed to a method for predicting whether or not a transplant recipient is likely to reject a tissue allograft comprising detection of IgG anti-HLA DR antibodies in the serum of the recipient *against a panel of control B lymphocytes* wherein detection of such antibodies indicates that the recipient is likely to reject a tissue allograft. In contrast, the Ten Hoor reference discloses assays wherein the recipients serum is tested for reactivity against only donor B-lymphocytes. That reactivity against donor B-lymphocytes (and also against donor T-lymphocytes) results in rejection is well known and is the reason that a donor-specific cross-match is always performed. If the cross-match is positive, the potential recipient does not receive that organ because of the increased risk of rejection and organ failure. The inventive step in claim 19 is the observation that, in the ABSENCE of a donor-specific positive B cell cross-match (since the specifications refer only to patients with negative donor-specific cross-matches), positive serum reactivity against a panel of control B lymphocytes which do not include B cells from the donor is predictive of subsequent rejection.

Given the difference between the subject matter of amended claim 19 and that of Ten Hoor, claim 19 cannot be rejected under 35 U.S.C.§102 (b). In view of the distinction between the cited art and the pending claims, the pending claims should be allowed to issue.

3.   Claim 19 is Not Obvious

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lazda (Transplantation, 57,964, 1994). The Examiner alleges that Lazda provides data suggesting that presence of IgG antibodies directed against HLA-DR antigens increases the risk of allograft rejection. While Lazda is not certain that anti-HLA class II (DR) antibodies are the mediators of rejection and thus teaches a need for further studies (page 967, col. 2), it would have been obvious for one to conduct further studies to confirm the findings of Lazda; the motivation to do so is explicitly provided by Lazda. The methods to conduct the studies are routine, and one would have had a reasonable expectation of success in so doing.

"...[A] proper analysis under §103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; **and** (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. "(emphasis added) *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).
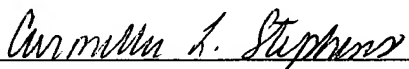
In the present instance, the relevant inquiry is whether one of ordinary skill in the art would have a reasonable expectation of success using a method for identification of patients at high risk for transplantation rejection based on the presence of IgG antibodies specific for class II antigens of the donor.

On page 967, column 2, lines 6-9 of Lazda it is stated that "the clinical significance of positive B-cell cross matches in renal transplantation continues to be *controversial*." Further, it is stated on page 968, column 1, lines 10-14 of Lazda that "although *antibodies to class II HLA antigens are usually not associated with hyperacute rejections* of renal allografts, several case reports exist of hyperacute rejection associated with these antibodies." Applicant maintains that given these statements set forth in the Lazda reference, one of ordinary skill in the art would not have had a reasonable expectation of success in practicing a method for identifying patients at high risk for transplantation rejection based on the presence of IgG antibodies specific for class II antigens of the donor. As a result, Applicant respectfully submits that the method of claim 19 is nonobvious. Thus, rejection should be withdrawn and the claims allowed to issue.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. Appendix I is submitted herewith, indicating the amendments to the claims and specification. The Applicants believe that the invention described and defined by the amended claims is patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

Carmella L. Stephens

Henry Tang
Patent Office Reg. No. 29,705
Attorney for Applicant(s)

Carmella L. Stephens
Patent Office Reg. No. 41,328
Agent for Applicant(s)

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APPENDIX I

IN THE SPECIFICATION:

On page 19, amend the first full paragraph as follows:

Coronary angiography in two planes was conducted at yearly intervals following transplantation for all patients without clinical features of coronary artery disease, or at unscheduled intervals if clinically indicated. Transplant-related coronary artery disease (TCAD) was difused as either [difused] diffused concentric narrowing of tertiary branches or significant obstruction of three or more major epicardial vessels.

On page 19, amend the paragraph immediately below the subheading 6.1.4.1 HLA TYPING as follows:

Serological typing of HLA-[L]A and HLA-B loci was performed by standard microcytotoxicity techniques. HLA-DR typing was performed by both serologic analysis and DNA techniques using sequence-specific oligonucleotide primers and the polymerase chain reaction.

On page 21, amend the paragraph immediately below the subheading 6.1.6 STATISTICAL ANALYSES as follows:

Kaplan-Meier univariate statistics were used to evaluate the relationship between cumulative high-grade rejection frequency and onset of TCAD, with p values calculated by log rank statistics (Kaplan, et al., 1958, J. American Statistics Association 53:457-481). Multivariable analysis of risk factors for a high-grade rejection over the 90 days following a low-grade EMB was performed using the Generalized Estimation Equations approach (Liang, et al., 1986, Biometrika 73:13-22) which incorporates a logistic regression model for the binary outcome, correcting for the correlation among observations in the same individual. For this

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analysis, events (high-grade rejections) were defined as the biopsy result nearest to 90 days following a low-grade biopsy. Variables considered as potential associated risk factors for a subsequent high grade rejection at the time of the low-grade biopsy included ischemic time, donor/recipient age, sex, race, matching at HLA-A, B, or DR loci, anti-HLA antibodies, and LGA. For variables determined to be associated with high-grade rejection in this analysis, positive and negative predictive values were evaluated using 2x2 contingency tables, as well as by Kaplan-Meier actuarial life tables. All data were analyzed using SAS [systm] system software (SAS Institute Inc., Cary, NC).

On page 23, amend the first paragraph as follows:

mismatched (odds ratio 2.42, p<0.0001), Figure 2. In contrast, donor/recipient matching at an [MCH] MHC class I locus (HLA-A or HLA-[13]B) did not influence progression to high-grade rejection (39% with no matches vs 36% for those with one or more matches, odds ratio 1. 16, p=0.35). The results validated our overall approach of identifying risk factors for progression of EMB to high-grade rejection, and enabled stratification of fully DR-mismatched recipients into a category requiring further immunologic monitoring.

On page 24, amend the paragraph immediately below the 6.2.5 subheading as follows:

The relationship between anti-HLA antibodies measured at the time of a low-grade biopsy and subsequent high-grade rejection was investigated. As shown in Table 3, the presence of circulating IgG antibodies against MHC class II molecules (IgG anti-[H]II) were associated with progression to a high-grade rejection within 90 days in individuals with complete donor-recipient HLA-DR mismatches, but not in those with at least one HLA-DR match. Among fully DR-mismatched individuals, 66% of low-grade EMBs accompanied by IgG anti-

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MHC class II antibodies progressed to a high-grade rejection compared with 42% of those without these antibodies (p < 0.01, odds ratio 2.68). Although in the initial analysis IgG anti-class I antibodies were associated with progression to high-grade rejection (odds ratio 1.92), this association in fact reflected the concomitant presence of IgG anti-MHC class II antibodies and was no longer evident after exclusion of individuals with IgG anti-MHC class II antibodies (progression to high-grade rejection occurred in 31% of EMBs with IgG anti-MHC class I antibodies vs 34% without IgG anti-MHC class I antibodies, p = 0.42, odds ratio 0.83). IgM anti-HLA antibodies were noted with subsequent high-grade cellular rejections.

On page 39, please amend Table 4. as follows:

Table 4. Multivariable equation describing the patient incremental factors associated with 90-day progression from a low-grade biopsy to a high grade rejection during the first year post cardiac transplantations.

	Odds ratio	95% CI	p value
positive LGA	4.34	1.73, 10.91	0.0018
positive [LgG] IgG anti-II	2.22	1,00, 5.02	0.0561
full DR mismatch	1.89	0.85, 4.27	0.1211

On page 1, insert as the first sentence of the specification following the title the following paragraph:

This application claims priority to PCT/US98/20887 filed October 2, 1998 which claims priority to provisional application 60/090,153 filed June 22, 1998 and provisional application 60/060,992 filed October 3, 1997.

Please amend Claim 1 as follows:

1.   (amended) A method for assessing the risk of transplantation rejection in [the] a recipient host comprising the following steps:

    (a)   determining the HLA-DR of the recipient and the HLA-DR of a donor and determining if the recipient and donor are DR mismatched;

    (b)   assaying for the presence of activated T-lymphocytes in the recipient;

    (c)   assaying for the presence of circulating IgG anti-HLA Class II antibodies in the serum of the recipient;

wherein the presence of activated T-lymphocytes in the recipient and the presence of circulating IgG anti-HLA Class II antibodies in a DR mismatched recipient indicates a high risk of transplantation rejection.

Please amend claim 19 as follows:

19.   (amended) A method for predicting whether or not a transplant recipient is likely to reject a tissue allograft comprising detection of IgG anti-HLA DR antibodies in the serum of the recipient against a panel of control B lymphocytes wherein detection of such antibodies indicates that the recipient is likely to reject a tissue allograft.

"the" not underlined

"a" not bracketed

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